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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,752	04/06/2006	Yunping Luo	TSRI 986.1	2531

2387 7590 04/14/2008

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
04/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,752	LUO ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Response filed on January 17, 2008 has been entered. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Q. Janice Li, at Group Art Unit 1633.

Election/Restrictions

The applicant's election without traverse of group I, and species election of DNA encoding polyubiquitianted FRa-1 and IL-18, is acknowledged. Upon search and consideration, the restriction requirement is hereby withdrawn.

Claims 1-65 are pending and under current examination.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 43-52 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The term "a transformed host cell" encompasses the situation where the cell is present or intended to be present in a human being, said cell becoming integrated into a human being and therefore being an inseparable part of the human itself. The scope of the claims, therefore, encompasses a

human being, which is non-statutory subject matter. As such, the recitation of the limitation "isolated" and/or "non-human" would be remedial. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a DNA vaccine comprising an attenuated *Salmonella typhimurium* comprising two separate plasmid encoding a polyubiquitinated Fra-1 and IL-18 respectively, and administering such via oral immunization for cancer gene therapy, wherein cancer cells overexpress Fra-1, does not reasonably provide enablement for using any polynucleotide encoding Fra-1 and IL-18, via any means of administration, for treating the type of cancer that does not overexpress Fra-1, wherein an effective anti-cancer immune response is achieved. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731,

737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

These claims are directed to compositions and methods of using such for cancer vaccination, which clearly or implicitly state the intended use of the composition and methods. With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. "DURING PATENT EXAMINATION, THE PENDING CLAIMS MUST BE 'GIVEN THEIR BROADEST REASONABLE INTERPRETATION CONSISTENT WITH THE SPECIFICATION'. *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 Fed. Cir. 2000" (MPEP 2111). "WHEN A COMPOUND OR COMPOSITION CLAIM IS LIMITED BY A PARTICULAR USE, ENABLEMENT OF THAT CLAIM SHOULD BE EVALUATED BASED ON THAT USE". (MPEP 2164.01c) When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. "A vaccine composition" "inhibiting tumor growth in a mammal" is defined as a composition for therapeutic use, to prevent, alleviate, treat, or cure cancer within the animal to which the substance is administered, therefore, will be evaluated by the standard.

The claims are drawn to cancer vaccine and method of using such for inhibiting tumor growth in a human patient. The specification teaches making a doubly attenuated aroA- dam- *S. typhimurium* transformed by two plasmid encoding polyubiquitinated Fra-1 protein and IL-18, respectively. The specification also teaches oral immunization of cancer-bearing mice with the doubly attenuated *S. typhimurium* protected mice against growth and metastases of breast cancer, wherein the cancer cells overexpress Fra-1.

Given the broadest reasonable interpretation, the instant claims encompass using any polynucleotide expressing Fra-1 and IL-18 for cancer vaccine, delivered via any route of administration. However, the state of the art teaches that the vector and the route of administration are critical for cancer gene therapy. For example, *McCluskie et al* (Mol Med 1999 May;5:287-300) teach "ROUTES OF ADMINISTRATION OF PLASMID DNA VACCINES INFLUENCES THE STRENGTH AND NATURE OF IMMUNE RESPONSES IN MICE AND NON-HUMAN PRIMATES." (See abstract) *Torres et al* (J Immunol 1997;158:4529-32) teach "TRANSFECTED CELLS IN GENE GUN-BOMBARDED SKIN, BUT NOT NEEDLE-INJECTED MUSCLE, PLAY A CENTRAL ROLE IN DNA-INITIATED AB AND CTL RESPONSE" (abstract). *Nakano et al* (J Virol 1997;71:7101-09) teach that immune reactivity with plasmid DNA encoding HCV-E2 antigenic domains is linked to the injection mode, "DIFFERENT ROUTES OF INJECTION OF HCV E2 PLASMID CAN RESULT IN QUANTITATIVELY AND QUALITATIVELY DIFFERENT HUMORAL IMMUNE RESPONSES" (see abstract). *Hurpin et al.* (Vaccine 1998;16:208-15) teaches the mode of p53 presentation, the type of vector, and route of administration are critical for the induction of immune response to p53 and antitumor immunity. *Hurpin et al.* teaches using a recombinant canaypox vector, intravenous, but not subcutaneous, intramuscular

or intradermal, administration induced CD8+ T lymphocytes capable of lysing tumor cells, while intradermal injection of a plasmid DNA encoding p53 leads to a complete protection against subsequent tumor challenge. Hence, one can not extrapolate from orally delivered *S. typhimurium*, to any and all types of polynucleotide via all routes of administration. Particularly considering *Liu* (Oncogene 2002;21:7680-9) teaches overexpressing mutant c-jun (another member of AP-1 transcription factors) leads to inhibition of breast cancer growth. *Urakami* (Biochem Biophy Res Comm 1997;241:24-30) teaches antisense oligos targeting AP-1 gene leads to tumor growth suppression. In view of such, delivering a polynucleotide overexpressing Fra-1 to the side of tumor or to circulation might have promoted tumor growth.

Moreover, as taught by *Powell et al.* (USP 6,682,729), the natural route of entry for *S. typhimurium* bacteria is mucosa, most commonly nasal and oral routes. It is unpredictable and the specification fails to teach the *in vivo* dynamics and consequences if the *S. typhimurium* is administered by any other route.

Further, each type of virus, bacteria vectors has different tissue tropism and each vector system have different in vivo dynamics, and efficiency in transducing different types of cells. Naked DNA is extremely inefficient in entry, and no mechanism for persistence or stability. (*Orkin et al,* Dec. 1995, pages 21-23, 30-32). Further, it was well known in the art, plasmid vectors have limited capacity to take in large size heterologous genes. Thus, when instant claims are directed to inserting at least two or more heterologous genes including Fra-1, IL-18, and IL-12 into a single plasmid

polynucleotide, it is highly likely that the plasmid would not efficiently express the inserted heterlogous genes.

The claims encompass inhibiting any type of tumor, while cancer immunotherapy is such that in order for tumor antigen specific T cells to be effective against the tumor, the tumor must be able to express recognizable levels of peptide/MHC class I complexes derived from tumor antigen(s). Since instant vaccine targets Fra-1, in the absence of Fra-1, it is unpredictable or unlikely the vaccine would be useful for suppressing tumors that do not overexpress Fra-1.

As to polyubiquitinated Fra-1, it may be one of the factors that led to the success on instant tumor suppression. *Rodriguez et al.* (J Virol 1998;72:5174-81) teaches ubiquitinated minigenes most probably requires polyubiquitination for improving performance of DNA immunization (e.g. the abstratct). Accordingly, it is unpredictable and the specification fails to teach that the claimed DNA vaccine without polyubiquitination would be sufficient for inhibiting tumor growth.

As to treating cancer in humans, although the mouse model has served as a useful tool for study cancer therapy, the artificially established tumor differs from the naturally occurring cancer in humans. *Bodey et al* (Anticancer Res 2000;20:2665-76) review cancer vaccines in cancer therapy, "THE THEORETICAL BASIS FOR ALL OF THESE APPROACHES IS VERY WELL FOUNDED. ANIMAL MODELS, ALBEIT HIGHLY ARTIFICIAL, HAVE YIELDED PROMISING RESULTS. CLINICAL TRIALS IN HUMANS, HOWEVER, HAVE BEEN SOMEWHAT DISAPPOINTING..."(page 2665, column one). The effective in mouse is not predictable in humans. "WHEN THESE VIRUSES WERE TRIED IN THE CLINIC, IT BECAME APPARENT THAT EXPERIMENTS IN ANIMAL MODELS HAD FAILED TO PREDICT KEY ASPECTS OF RECOMBINANT VACCINE

FUNCTION IN PEOPLE" (*Yu & Restifo*, J Clin Invest 2002 Aug;110:289-94, paragraph bridging the right column in page 291). "WE DO NOT YET HAVE A CANCER VACCINE IN HAND THAT CAN RELIABLY INCREASE PATIENT SURVIVAL OR INDUCE TUMOR DESTRUCTION". *Cao et al* (Stem Cells 1998;16:251-60) review cytokine gene transfer in cancer therapy, they highly appreciate the potential of such approach and how studies in animal models could provide valuable information for planning clinical studies, they go on to teach "ANIMAL MODELS ARE UNABLE TO ACCURATELY REPRODUCE THE COMPLEXITY AND VARIABILITY EXHIBITED AMONG CANCER PATIENTS", "THE THERAPEUTIC EFFICACY OF THESE APPROACHES, HOWEVER, REMAINS TO BE DEMONSTRATED" (3rd paragraph on page 255).

One can not extrapolate the teachings of the specification to the scope of the claims because without undue experimentation, the skilled artisan cannot predict the in vivo dynamics and consequences on tumor growth when any polynucleotide is used and administered via any route. It would have required undue experimentation for one of skilled in the art to achieve the intended results for cancer therapy.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims, it would have required undue experimentation to practice the invention as they generically claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 61 and 63 are rejected under 35 U.S.C. 102(e) as being anticipated by *Kleanthous et al.* (USP 6585975).

Kleanthous teaches a method involving mucosal (orally) administration of an attenuated *Salmonella* vector comprising a nucleic acid molecule encoding a Helicobacter antigen (column 1, lines 32-45), and preferably, co-administered with a suitable adjuvant (see e.g. the abstract), wherein the adjuvant may be a cholera toxin (CT) or an E. coli heat-labile toxin (LT), which is an immune stimulating molecule (see e.g. paragraph bridging columns 5-6). *Kleanthous* teaches many forms of attenuated *S. typhimurium* were known in the art (see e.g. paragraph bridging columns 2-3, & fig. 3), including the Dam (DNA methylation), and auxotrophic mutations, such as mutations in any of the aroA, aroC, aroD (aromatic compounds). Accordingly, *Kleanthous* anticipates instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 61-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Rosenkranz et al.* (Vaccine 2003;7:798-801), in view of *Powell et al.* (USP 6682729), and *Kleanthous et al.* (USP 6585975).

Rosenkranz teaches a method of delivering IL-18 via attenuated *S. typhimurium* (e.g. the abstract), wherein the IL-18 may be co-administered with a tumor antigen to enhance antitumor effect (e.g. § 5). *Powell* teaches delivering tumor antigen to cancer patients using attenuated *S. typhimurium* (e.g. claim 1), which may be aroA-, wherein the aroA- *S. typhimurium* may contain other mutations. *Powell* also teaches that it is not critical which attenuated strains were used (column 13, lines 23-33). *Kleanthous* teaches both Dam^- and $aroA^-$ mutations to attenuate *S. typhimurium* were known in the art (see e.g. paragraph bridging columns 2-3, & fig. 3).

In view of above considerations, it appears all the recited elements were known in the art, and hence "THE COMBINATION OF FAMILIAR ELEMENTS ACCORDING TO KNOWN METHODS IS LIKELY TO BE OBVIOUS WHEN IT DOES NO MORE THAN YIELD PREDICTABLE RESULTS." *KSR*, 127 S. Ct. at 1740, 82 USPQ2d at 1395-96. Accordingly, it would have been obvious for the skilled artisan to deliver a tumor antigen along with an immune stimulatory molecule with a doubly attenuated aroA- dam- *S. typhimurium*, with a

reasonable expectation of success.

Citation of Relevant Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. *Darnell* (Nat Rev Cancer 2002;2:740-9) teaches targeting transcription factors for cancer therapy, including generating antibodies blocking cell-surface receptors. However, Fra-1 is located in the cytoplasma and nucleus; it is unpredictable whether oral Fra-1 vaccination would generate sufficient mechanism to inhibit Fra-1 function, or leading to suppression of tumor growth. Thus, the prior art of record fail to teach or expect a reasonable success of the instantly claimed invention.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7:30 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

April 11, 2008